REMARKS UNDER 37 CFR § 1.111

Formal Matters

This paper is responsive to the Office Action dated September 26, 2002 (Paper No. 10), which is the first action on the merits of the application.

Claims 33-58 are pending in the application. Claims 33, 35-40, 45, 51, and 53-58 are under examination, and stand variously rejected.

Support for the amendments made herein are found in the specifcaiton at, for example, page 11, lines 29-30; and page 14, lines 12-25.

Reconsideration and allowance of the application is respectfully requested.

No new matter is added.

Request for Rejoinder and Claim Objections:

In co-pending application 09/700,354, applicants are petitioning against the restriction made between different SEQ. ID NOs listed in the disclosure. The basis of the petition is that MPEP § 803 prohibits restriction where it would not be a burden on the Office to examine the subject matter together — whether or not more than one independent or distinct inventions are covered. No burden is imposed in the '354 application, because the sequences have all been searched in priority application 09/081,385.

The specification of the '354 application is the same as that of the present application, and the issues respecting division between the SEQ. ID NOs are the same. Upon adjudication of the Petition in applicant's favor, it would be appropriate to rejoin all of the sequences claimed in this application be rejoined into the group under examination, for the same reason. To facilitate the Examiner's review of the subject matter, and to prevent unnecessary delay in obtaining patent protection for this invention, applicants respectfully urge that all pending subject matter in this application be rejoined into the group under examination as soon as possible.

Claims 35, 39 and 40 were objected to as containing limitations drawn to non-elected inventions. In view of the above, applicants respectfully request this objection be held in abeyance.

Objection to the Specification

The Office Action objects to the specification on the ground that it lacks an abstract on a separate sheet. However, applicants filed such an abstract as the last page of the specification, which is numbered page 100. The return post card filed with the application indicates the specification as filed had 100 pages. The Examiner is respectfully requested to contact the undersigned should the Office's file differ from that of applicants.

Rejections under 35 USC § 112 ¶ 1:

Claims 35, 39, 40, 45, and 51 stand rejected under § 112 ¶ 1 as not being adequately described by the specification (Office Action page 5).

Applicants respectfully disagree. The "Revised Interim Written Description Guidelines" of the U.S. Patent & Trademark Office indicates that a claim to polynucleotides related by the ability to hybridize to a single representative polynucleotide meets the written description requirements of § 112 ¶ 1. Claim 35 (and its dependents) as previously presented and as amended comport exactly with Example 9 of the guidelines.

Claims 35, 39, 40, 45, and 51 also stand rejected under § 112 ¶ 1 on the basis that the specification is enabled for producing a protein from SEQ. ID NO:9, but not from closely related variant polynucleotides that hybridize under stringent conditions to SEQ. ID NO:9. (Office Action page 3 and page 4)

Applicants respectfully disagree for the following reasons:

- The Office has not established a prime facie case for lack of enablement
- Variants of the representative species (SEQ. ID NO:9) that encode TRRE activity can be made without undue experimentation
- The Office has an established policy of issuing patents with claims covering variants of a single representative species

A: No prima facie case for lack of enablement:

The Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention[1]. This burden has not been met.

In making the rejection, the Office indicates that the specification fails to provide performance parameters of any of the possible [variants] of the protein encoded by SEQ. ID NO:9.

To the contrary. Page 29-34 of the specification provides detailed instructions for a suitable assay for measuring TRRE activity. If a protein has significant activity when measured in this assay, then it will meet the functional requirement of the claim. Variant proteins produced from the polynucleotides indicated, and capable of causing release of TNF receptor from human cells, will fulfill the requirements of the claim. On the other hand, variants that do not cause release of TNF receptor from human cells will fall outside the claim. Accordingly, testable parameters for working variants are provided in the claim, and an exemplary assay is provided in the specification.

The rejection made in the Office Action relies in part on the assertion that it is not possible to predict with absolute certainty which of the variants will work. This assertion is inadequate to support a prime facie case for lack of enablement. Absence of complete predictability only means that the ultimate proving of functional variants is a matter of empirical testing — *not* that such variants are hard to find.

In particular, a paper by Voet et al. (1990) is cited as indicating that a single substitution in a hemoglobin molecule will affect its function. This does not establish a *prima facie* case, because it is only one out of 19 possible variations at one out of 146 possible positions. In other words, the paper teaches that one variant (with the Glu at this position) works in a native manner, while one variant (with the Val at this position) works in a different manner. In theory, there are about 2772 other possible variants with one amino acid change. The evidence offered by the

---

[1] *In re Wright,* 27 USPQ 2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.04.

Patent Office does not indicate the proportion of the other variants (if any) that lack native activity. Indeed, as far as we know, virtually all of them may work quite well.

Nature provides many illustrations showing that a wide range of alterations are tolerated at almost all positions of working proteins. Protein sequences are typically *only ~70% identical* between different mammalian species. This indicates that a wide range of substitutions are possible without affecting function. Indeed, there is no reason why the skilled reader could not make as n=many functional variants of TRRE that they desire.

B: Variants may be obtained by routine experimentation

There are a number of methods available to construct variants of the TRRE sequence. The Office Action implies that the user would want to create variants by making deliberate changes to SEQ. ID NO:9, as described above. Deliberate point mutations are sometimes made when the investigator wants to map functional elements within the primary protein structure.

Although the reader may wish to make variants by mutation at particular sites, it is unnecessary for them to do so. Where the object is only to generate functionally equivalent variants, the skilled reader can employ a random mutation strategy, which is even more straightforward. There is an enormous literature in the art relating to introducing mutations of various kinds. The standard texts *Protocols in Molecular Biology* (Ausubel et al. eds.) and *Molecular Cloning: A Laboratory Manual* (Sambrook et al. eds.) describe techniques employing chemical mutagenesis, cassette mutagenesis, degenerate oligonucleotides, mutually priming oligonucleotides, linker-scanning mutagenesis, alanine-scanning mutagenesis, and error-prone PCR. Other efficient methods include the E. coli mutator strains of Stratagene (Greener et al., Methods Mol. Biol. 57:375, 1996) and the DNA shuffling technique of Maxygen (Patten et al., Curr. Opin. Biotechnol. 8:724, 1997; Harayama, Trends Biotechnol. 16:76, 1998).

The mutated variants can then be cloned out and tested for functionality as described in the specification. To the extent that the user may wish to test variants near the outer limit of variability in the claims (i.e., only ~90% identical to SEQ. ID NO:9), they may subject the representative sequence to successive cycles of mutation and functional testing — or choose a mutation strategy that generate more abrupt changes, such as the DNA shuffling technique.

To what extent will the variants produced by these techniques have the required functional activity? The Office Action cites *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) as setting the standard for unreasonable experimentation. In fact, the patent under consideration was found to be *enabling* for production of the genus of monoclonal antibodies having the specificity and affinity claimed[2]. The screening of TRRE variants for function according to the present invention is routine in the same manner as testing hybridoma clones for secretion of antibody with particular characteristics.

In summary, generating variants of the representative sequence SEQ. ID NO:9 can be done by standard techniques in the art. The variants can be tested for functionality by a number of suitable assays, such as those described in the specification. The evidence of record in this application and presented in this Response implies that a substantial proportion of these variants will have TRRE catalytic activity, and can be made and identified without undue experimentation.

C: The Office has an established policy of allowing coverage for closely related sequences

As referred to earlier, the "Revised Interim Written Description Guidelines" indicates that polynucleotide sequences claimed according to their ability to hybridize to a representative sequence fall within the description requirements of 35 USC § 112 ¶ 1. It is inconceivable that the Office would have promulgated these Written Description Guidelines knowing that this illustration complied with the description requirements of § 112 ¶ 1, but not the enablement requirements of the very same statute.

At the time of this writing, there are approximately 1946 issued U.S. patents that have the words "stringent" and "hybridize" or "hybridization" in the claims. The Office is especially invited to consider U.S. Patent 6,413,741, which issued this past July. Claim 1 covers nucleic acid encoding a polypeptide monomer that has the ability to form, with at least one additional

---

[2] In *Wands*, the patent application claimed monoclonal antibodies of a particular specificity and affinity. The PTO contended that only 2.8% of the hybridomas obtained were proven to fall within the claim, and thus the claim was not enabled. *The Court held that the application was fully enabled for the claimed subject matter*, because it was standard practice to screen negative hybridomas in order to find one that makes the desired antibody. 8 USPQ2d at 1406-07.

alpha subunit, a potassium channel having the characteristic of voltage gatin[g], wherein said nucleic acid specifically hybridizes under [specified] stringent conditions to SEQ ID NO:2. The Examiners listed on the cover of the patent are Joseph F. Murphy and David S. Romeo.

It would be unfair to hold applicants of the present application to only the exact sequence obtained. This would give competitors an easy way to steal the essence of applicants' discovery simply by making a close functional variant with one or more mutations in the sequence. The objective would be not to improve the properties of the molecule, but simply to evade applicants' patent protection.

The case law provides the following commentary on the public policy reasons for allowing applicants reasonable claim scope beyond the species explicitly disclosed:

> To require such a complete disclosure [of all the species claimed] would apparently necessitate a patent application or applications with thousands of catalysts . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used . . . [3]

The TRRE sequences provided in this disclosure represents a new discovery of an important new gene family with important biological activity. The coverage scoped out by the claims in the present application circumscribe a reasonable area of coverage that is necessary to adequately protect against easy and insubstantial work-around variants — in full accordance with the standard set in *Angstadt.*

Withdrawal of the rejections under 35 USC § 112 ¶ 1 is respectfully requested.

---

[3] *In re Angstadt,* 190 USPQ 214 at 218 (CCPA 1976)

Rejections under 35 USC § 112 ¶ 2:

Claims 35, 40, and 51 are rejected for not specifying what is meant by the term "stringent hybridization". Applicants respectfully disagree, since the term is defined on page 11 of the specification. Nevertheless, as a courtesy to the reader, the hybridization conditions have been explicitly incorporated into claim 35. Since this does not change the definition of the term, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Claim 33 and its dependents are rejected for not defining the term "TRRE". In fact, a term is not indefinite with respect to the requirements of § 112 ¶ 2 when the meaning of the term is explained in the specification. In this case, the specification both expands and defines the meaning of the term TRRE. However, for the convenience of the reader, applicants have amended claim 33 to remove the abbreviation objected to. Since this does not change the definition of the term, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Withdrawal of these rejections is respectfully requested.

Rejections under 35 USC § 102 and § 103:

Claims 33, 37-38, 53-56, and 58 stand rejected under 35 USC § 102(b) as being anticipated by Katsura et al., Biochem. Biophys. Res. Commun. 222:298, 1996. The same claims and additionally claim 57 stand rejected under 35 USC § 103(a) as being obvious over Katsura et al., in view of Björnberg et al., Scand. J. Immunol. 42:418, 1995.

In order to distinguish the invention claimed in this application from the Katsura reference, claim 33 has now been amended to require that the polypeptide used in the claimed screening method be present in the incubation mixture in *isolated* form. Katsura et al. detect TRRE activity in the THP-1 cell line, but they do not teach or suggest a method for isolating it. Björnberg et al. detected TNF receptor shedding in two cell lines, but do not teach or suggest a method for isolating the proteases that are responsible for the observed activity.

It is well established in the case law that a reference must be enabling for the claimed subject matter if it is to constitute a bar to patentability under 35 USC § 102(b)[4]. In the present application, the cited references cannot be patent defeating for the claimed screening method, since they do not place into the hands of the public the TNF receptor releasing enzyme in an isolated form[5].

It is a well-established standard in the U.S. Patent & Trademark Office that a description of a biological activity does not prevent the patenting of the molecules responsible for the activity once they are isolated and characterized — or their use in isolated form for any purpose. Indeed, the usual course in biomedical research is that description of an important biological activity comes first, and the molecules responsible for the activity are discovered at a later time, after considerable inventive effort. If patentability was barred as soon as a biological activity was described, *then it would rarely be possible to patent such biologically important molecules as hormones, growth factors, cytokines, inflammatory mediators, cancer resistance factors, and cell-surface receptors for a large variety of signal transducers and effectors.* Such an arbitrary standard in turn would remove the incentive for pharmaceutical companies to develop important therapeutic modalities.

By way of illustration, consider the history of discovery of the TNF Receptor itself. Before the receptor was isolated, TNF-α and TNF-β (ligands for the receptor) had been cloned and sequenced, and a number of their important metabolic effects of these cytokines on cells had been described. It was therefore inevitable that cells responding to TNF had a TNF receptor.

---

[4] References relied upon to support a rejection under 35 USC § 102(b) or § 103 must provide an enabling disclosure, placing the invention in the possession of the public. *Beckman Instruments, Inc. v. LKB Produckter AB,* 13 USPQ2d 1301 (Fed. Cir. 1989); *Chester v. Miller*15 USPQ2d 1333 (Fed. Cir. 1990). "We think it is sound law, consistent with the public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." *In re LeGrice*, 133 USPQ 365 at 372 (CCPA 1962). In the case at issue in *LeGrice*, a rosa floribunda plant was held to be patentable, even though a photograph showing the characteristics of the rose had been published in a catalog more than a year before the critical date.

[5] Applicants disagree that the references adequately suggest the screening of unknown compounds, or that there is motivation to combine them in the fashion indicated in the Office Action. Furthermore, applicants have not determined whether the cited references adequately meet all the limitations of dependent claims 37-38 and 53-58. It is unnecessary to provide further commentary on these issues, since the rejection can be overcome just by showing the cited references do not place isolated TRRE in the hands of the public — which makes any use of the isolated enzyme non-obvious.

There were a large number of studies published showing that TNF receptor activity resided on a variety of cell types:

- Aggarwal et al. "Characterization of receptors for human tumour necrosis factor and their regulation by gamma-interferon." Nature 318:665, 1985.
- Kull et al. "Cellular receptor for ^{125}I-labeled tumor necrosis factor: specific binding, affinity labeling, and relationship to sensitivity." Proc. Natl. Acad. Sci. USA 82:5756, 1985.
- Baglioni et al. "Binding of human tumor necrosis factor to high affinity receptors on HeLa and lymphoblastoid cells sensitive to growth inhibition." J. Biol. Chem. 260:13395, 1985.
- Tsujimoto et al. "Characterization and affinity crosslinking of receptors for tumor necrosis factor on human cells." Arch. Biochem. Biophys. 249:263, 1986.
- Yoshie et al. "Binding and crosslinking of ^{125}I-labeled recombinant human tumor necrosis factor to cell surface receptors. J. Biochem. (Tokyo) 100:531, 1986.
- Holtmann & Wallach. "Down regulation of the receptors for tumor necrosis factor by interleukin 1 and 4 beta-phorbol-12-myristate-13-acetate." J. Immunol. 139:1161, 1987.
- Yonehara et al. "A cell-killing monoclonal antibody (anti-Fas) to a cell surface antigen co-downregulated with the receptor of tumor necrosis factor." J. Exp. Med. 169:1747, 1989.

In particular, Aggarwal et al. used labeled TNF-α in an assay method to study binding to the human cervical carcinoma line ME-180. They found that there was a single class of specific high-affinity receptors, and described the affinity of the receptors and the number on each cell. They also described the use of interferon-γ to increase the receptor density on the cell surface. Yoshie et al. describe an assay in which they cross-linked labeled TNF to receptors on HeLa and THP-1 cells. The data provide an estimate of the affinity, receptor number, and the molecular weight of the receptor.

Subsequently, Smith et al. at the Immunex Corporation isolated the p75 TNF receptor and determined aspects of its structure. The priority patent application was filed on September 5,

1989, which post-dates all the publications listed above. Nevertheless, broad patent protection for the isolated p75 TNF receptor protein was granted to Immunex in U.S. Patent 5,945,397.

As reviewed in the Background section of this application, evidence for TNF-receptor shedding and its biological importance has been appreciated for some time:

- Porteu et al. "Shedding of tumor necrosis factor receptors by activated human neutrophils." J. Exp. Med. 172:599, 1990.
- Schall et al. "Molecular cloning and expression of a receptor for human tumor necrosis factor." [Relation between membrane TNF-R and the soluble form] Cell 61:361, 1990.
- Aderka et al. "Increased serum levels of soluble receptors for tumor necrosis factor in cancer patients." Cancer Res. 51:5602, 1991.
- Gullberg et al. "Involvement of an Asn/Val cleavage site in the production of a soluble form of a human tumor necrosis factor (TNF) receptor. Site-directed mutagenesis of a putative cleavage site in the p55 TNF receptor chain." Eur. J. Cell Biol. 58:307, 1992.
- Brakebusch et al. "Cytoplasmic truncation of the p55 tumour necrosis factor (TNF) receptor abolishes signaling, but not induced shedding of the receptor." EMBO J. 11:943, 1992.
- Grosen et al. "Measurement of the soluble membrane receptors for tumor necrosis factor and lymphotoxin in the sera of patients with gynecologic malignancy." Gynecol. Oncol. 50:68, 1993.
- Halwachs et al. "Serum levels of the soluble receptor for tumor necrosis factor in patients with renal disease." Clin. Invest. 72:473, 1994.
- Redl et al. "Tumor necrosis factor (TNF) dependent shedding of the p55 TNF receptor in a baboon model of bacteremia." Infect. Immun. 63:297, 1995.
- Diez-Ruiz et al. "Soluble receptors for tumour necrosis factor in clinical laboratory diagnosis." Eur. J. Haematol. 54:1, 1995.

Nevertheless, the cited references do not tell the public how to go about cloning or isolating the responsible protease. In spite of the recognized importance of TNF receptor shedding in cancer, bacteremia, and a number of other clinical conditions, no one else succeeded

in isolating the protease before the filing of the current series of patent applications by Gatanaga and Granger.

This underscores the inventive nature of the isolated TRRE preparations disclosed in this application[6]. The two cited references do not render obvious the invention claimed in this application, any more than the Aggarwal or Yoshie assay methods anticipated isolation of the TNF receptor.

In fact, isolation of an enzyme is a more difficult task than isolating a receptor, because of the amount of protein involved in the biological effect. If there are 2,000 to 100,000 TNF ligand binding sites on a cell surface (as described by Aggarwal and Yoshie), then there would be ~2,000 to 100,000 receptors on the membrane (a stochiometric amount). In contrast, a single TNF receptor protease molecule may cause the shedding of more than 5, 50, or 500 receptors (a catalytic amount). This means that relatively few enzymatic molecules may be needed for the observed biological effect — perhaps only a handful of copies per cell. Clearly, the task of isolating such a rare molecule is much more formidable.

The methods disclosed in this application overcome these problems, providing isolated and recombinant TNF receptor protease for use in drug screening, and for other commercially important applications, such as the treatment of arthritis. This is both novel and non-obvious, and therefore complies with the patentability requirements of 35 USC § 102 and § 103.

Withdrawal of these rejections is respectfully requested.

---

[6] That the claimed invention unexpectedly solved longstanding problems supported the conclusion of nonobviousness. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

Conclusion

Applicants respectfully request that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicants hereby request an interview by telephone.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-007CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 21, 2003

By: _____
Carol L. Francis
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\IRVN (UC Irvine)\007con2\Resp to oa (09-26-02) pto.doc